The Translational Research Acceleration Initiative

Clinical Trials and Translational Research Advisory Committee

November 4, 2009

Lynn M. Matrisian
Special Assistant, NCI
How can we best assure that:

- The most promising concepts enter the developmental pathways?
- Concepts that do enter advance to the clinic or to productive failure?
- Progress is as rapid, efficient and effective as possible?
Coordinated Management
- Integrated NCI management
- Budget designation
- TR coding
- Prioritization process

Tailored Funding
- Modify TR award mechanisms
- Improve investigator-initiated TR awards
- STRAP awards
- Academic/industrial collaborations

Operational Effectiveness
- Project management
- Core services coordination
- Enhance biorepositories
- Improve IP negotiations
- Enhance foundation/advocate group collaborations
- Enhance training/incentives

Optimize and enhance NCI functions that are critical for translational research

Develop a new process to accelerate translational cancer research

www.cancer.gov/trwg
Select several projects/year that are “ripe” for translation

- Translational Research Acceleration Process DOES:
  - Gather information on translational opportunities
  - Prioritize translational research opportunities
  - Develop a funding & project management plan to accelerate prioritized opportunities

- Translational Research Acceleration Process DOES NOT:
  - Impact Discovery research
  - Replace existing infrastructure or mechanisms for clinical or translational research
NCI’s Clinical Trials and Translational Research Advisory Committee (CTAC) recommended that NCI proceed with establishing a process to accelerate translational cancer research (Dec 08):

- Gather information
- Prioritize
- Fund & Manage

Immune Response Modifier Pathway Pilot Project
Piloted information gathering and prioritization with Immune Response Modifier Pathway

- Most complex of the Pathways
- Previous prioritization of Immune Response Modifiers (summer 2007)

- A group of committed immunologists/immunotherapists could be identified (Mac Cheever, Fred Hutchinson Cancer Center)

- Phase I: Focused on Antigen development
- Phase II: Expanded to entire IRM Pathway
Immune Response Modifier Pilot Prioritization Process

Project: Antigens (Phase I)

• Purpose: To develop a well-vetted ranked priority list of cancer vaccine target antigens based on pre-defined and pre-weighted objective criteria

• Process
  – Developed list of “ideal” cancer antigen criteria/characteristics
    • Email
      • 36 experts
  – Prioritized and weighted criteria using pair-wise comparisons
    • Web-based, Sept 2008
      • 20 experts
  – Selected 100 representative antigens
  – Assembled information on pre-defined criteria from experts for each antigen
    • ~79 experts, final 75 antigens
  – Ranked antigens based on the pre-defined pre-weighted criteria
    • Face-to-face, Oct 2008
      • 16 reviewers

Clin Can Res, 15: 5323, 2009
The IRM Subgroup of the Process to Accelerate Translational Science (PATS) Working Group of CTAC

• Purpose: To pilot the prioritization of IRM Pathway Translational Research Opportunities using pre-defined and pre-weighted objective criteria

• Process
  – Developed list of “ideal” criteria/characteristics for IRM Pathway Translational Research Opportunities based on the IRM Pathway and the previous Antigen Prioritization experience
  – Prioritized and weighted criteria using pair-wise comparisons
    – Web-based pilot prioritization (4 extramural investigators)
    – Face-to-Face meeting April 19, 2009 at AACR (21 investigators)
    – Subsequent facilitated or asynchronous web sessions (15-21 votes/category)
IRM Subgroup of the PATS
Working Group members:

Co-Chairs
Martin A. Cheever, Fred Hutchinson
Lynn Matrisian, NCI

James Allison, Mem. Sloan-Kettering
Lisa Butterfield, Univ. of Pittsburgh
Nora Disis, Univ. of Washington
Olivera Finn, Univ. of Pittsburgh
Bernie Fox, Providence CC
Dmitry Gabrilovich, Moffitt CC
Thomas Gajewski, Univ. Chicago
Toby T. Hecht, NCI
Elizabeth Jaffee, John Hopkins
Francesco Marincola, NIH

Svetomir Markovic, Mayo
Ira Mellman, Genentech
Karolina Palucka, Baylor
David Peace, Univ. Illinois
Nickolas Restifo, NCI
Jeffrey Schlom, NCI
Howard Streicher, NCI
Mario Sznol, Yale Univ
Walter Urba, Providence CC
Jeffrey Weber, Moffitt CC
Louis Weiner, Georgetown
Jedd Wolchok, Mem. Sloan-Kettering
Analytical Hierarchy Process (AHP): A structured technique for complex decision making

- Based on mathematics and human psychology
- Provides a comprehensive framework
  - To structure the problem
  - To represent and quantify key elements
  - To relate those elements to overall goals
  - To evaluate alternative solutions

Saaty, T.L., 1970’s
IRM Pathway Criteria and Subcriteria
(IRM SG of PATS WG)

Pathway Components:
- Target (Antigen/Antibody/T-cell)
- Formulation (cell preparation, delivery vehicle, adjuvant, etc)
- Immune Modifier Agent (cytokines, etc)
- Combination Regimen
- Assay for Immune Response
- Assay to select patient population
- Availability of Patients for Trials

Scientific Validity & Feasibility for each component
Rating scales/level of evidence for each criteria
Pre-determined, weighted criteria for IRM prioritization

<table>
<thead>
<tr>
<th>CRITERIA Subcriteria</th>
<th>RATING SCALE</th>
<th>LEVEL OF EVIDENCE in descending order</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IMMUNE MODIFIER AGENT (cytokines, etc)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scientific validity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Augments specific immunity in human trials</td>
<td>Data for augmenting specific immunity in human trials is superb as judged by an informed expert</td>
<td>Data for augmenting specific immunity in human trials is adequate</td>
</tr>
<tr>
<td>Augments specific immunity in animals</td>
<td>Data for augmenting specific immunity in animals is superb as judged by an informed expert</td>
<td>Data for augmenting specific immunity in animals is adequate</td>
</tr>
<tr>
<td>Augments specific immunity in vitro</td>
<td>Adequate data for augmenting specific immunity in human cells in vitro</td>
<td></td>
</tr>
<tr>
<td>No in vitro or in vivo data available</td>
<td>No in vitro or in vivo data available</td>
<td></td>
</tr>
<tr>
<td>Feasibility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturing of clinical grade agent</td>
<td>GMP/clinical grade manufacturing of the agent at scale is reproducible and reliable</td>
<td>Scalable clinical grade manufacturing process for the agent has been piloted</td>
</tr>
<tr>
<td>Manufacturing of clinical grade class-related modifier</td>
<td>Scalable clinical grade manufacturing process for the agent class has been demonstrated</td>
<td></td>
</tr>
<tr>
<td>Available as a laboratory grade product</td>
<td>Laboratory product only</td>
<td></td>
</tr>
<tr>
<td>Not developed</td>
<td>Not completely developed</td>
<td></td>
</tr>
</tbody>
</table>
Gather information

Prioritize

Fund & Manage
Gather IRM Translational Research Opportunities

Request for Information (RFI): Immune Response Modifiers Pathway Translational Research Opportunities

Notice Number: NOT-CA-09-031

Key Dates
Release Date: July 30, 2009
Response Date: Responses must be received by August 24, 2009

Issued by
National Cancer Institute (NCI) [http://www.cancer.gov/]

This is a Request for Information (RFI). It is to obtain knowledge and information for project planning purposes only and should not be construed as a solicitation for grants, contracts, etc.

Purpose and Objectives

This RFI is to gather information from the scientific community regarding opportunities in cancer immunotherapy and immunoprevention that could benefit from accelerated development through focused funding and coordinated management. This request is part of the NCI's new Process to Accelerate Translational Science as recommended by the Translational Research Working Group (TRWG). At the discretion of the NCI, the information gathered in response to this RFI may be used in a variety of ways by the NCI, including but not limited to: 1) assist NCI in the development of Requests for Proposals (RFPs), Requests for Applications (RFAs), Program Announcements (PA), Cooperative Research and Development Agreements (CRADA), Cooperative Agreements, and/or other mechanisms/agreements; 2) assist in developing formulations, production and implementation of products/devices/processes, using existing internal NCI mechanisms, to include but not limited to in-house staff, contracts, grants, cooperative agreements, etc.; or 3) no action taken.

Background

This TRWG was an NCI-sponsored working group charged with evaluating the status of the NCI's investment in translational research and envisioning its future in an inclusive, representative, and transparent manner. In 2007, the NCI accepted the TRWG recommendations to accelerate translational cancer research as outlined in the report entitled “Transforming Translation: Harnessing Discovery for Patient and Public Benefit” [http://www.cancer.gov/tstrap].

One of the TRWG recommendations was the establishment of a year-round process to identify a small number of opportunities for specific cancer treatments, prevention or assessment modalities that are “ripe” for further development, and then to provide the funding or resources as well as the project management required to advance these opportunities as rapidly as possible to early stage clinical trials. This recommendation is being implemented and includes a prioritization process to identify and rank individual translational research opportunities, the provision of dedicated project management resources for the resulting prioritized projects, and the development of project-specific funding approaches for these new, prioritized Special Translational Research Acceleration Projects (STRAPs).

The Process to Accelerate Translational Science was initiated with the first NCI Translational Science Meeting, held November 7-8, 2008 [http://shieldsavante.nci.nih.gov/]. This meeting educated the translational cancer research community about the TRWG Pathways to Clinical Goals (Clinical Cancer Research 14: 1593-1574, 2008, http://ncipress.oneworldjournal.com/content/14/17/1593.full.html) and demonstrated that there are compelling translational research opportunities that warrant acceleration. The Pathways to Clinical Goals describe the steps required to create a treatment, prevention or assessment modality based on advances in scientific knowledge, and develop that modality to the point of early phase clinical trials. The term “Translational Research Opportunity” refers to a developmental project that follows one of these six TRWG Pathways (Agent, Immune Response Modifier, Intervention Device, or Lifestyle Alteration Intervention, or Biomarker-Based or Imaging-Based Assessment Tool), and identifies the patient/cancer type in which it is to be tested.

Information Requested

This RFI invites input from the scientific community on Translational Research Opportunities that follow the Immune Response Modifiers Pathway to testing in Phase II clinical trials (Clinical Cancer Research 14: 1593-1574, 2008, http://ncipress.oneworldjournal.com/content/14/17/1593.full.html). Information is sought from members of the scientific community at large, academic and nonacademic translational cancer researchers, clinical oncologists, and investigators from the pharmaceutical industry. The opportunities can relate to a range of specific therapeutic regimens and target populations. Any information that can be shared regarding the immunogenicity and therapeutic function of an antigen, the scientific validity and feasibility of the formulation for that antigen, and/or the scientific validity and feasibility of combinations with immune modifier agents is requested. In addition, information on essays of
NCI-wide Translational Science Meeting

- November 7-9, 2008, Washington, DC
  - 513 posters
    - Grants/PIs selected by NCI program staff
  - 800 invited participants
    - NCI-funded scientists/clinicians
    - Advocates
    - NCI staff

- TSM2: November 5-7, 2009, Vienna, VA
  - 423 posters
  - >750 participants
  - Added cross-pathway Panel Discussion sessions
  - Added open Satellite meetings

Gather IRM Translational Research Opportunities: TSM and TSM2

23 IRM abstracts

20 IRM abstracts
Gather information

Prioritize
Which Opportunities are most “ripe” for acceleration?

Fund & Manage
IRM Prioritization Working Group of CTAC

- Lisa Butterfield, *Univ Pittsburgh*
- **Mac** Cheever, *Fred Hutchinson*
- Nora Disis, *Univ Washington*
- Olivera Finn, *Univ Pittsburgh*
- Elizabeth Jaffee, *Johns Hopkins*
- Carl June, *Univ Penn*
- David Peace, *Univ Illinois*
- Jane Reese-Coulbourne, *Advocate Partners*
- Wenru Song, *Pfizer*
- Mario Sznol, *Yale Univ*
- Louis Weiner, *Georgetown*
- **Jay** Berzofsky, *NCI CCR*
- Francesco Marincola, *NIH CC*
- Nicholas Restifo, *NCI CCR*
- Giorgio Trinchieri, *NCI CCR*
- *Stephen** Creekmore, *NCI, BRB*
- *Toby** Hecht, *NCI, TRP*
- *Howard** Streicher, *NCI, CTEP*
- *Lynn** Matrisian, *NCI, CCCT*
- *Tawab** Amiri, *NCI, CCCT*

* NCI liaisons
• Web-based platform facilitates webinar discussion or asynchronous input
• Logical organization and tracking of alternatives
• Facilitates updates in information
• Facilitates transparency, discussion of disparate viewpoints
• Integrates objective and subjective evaluation
• Allows “what if” scenarios to increase confidence in ranking
• Allows evaluation of components in isolation
• Does NOT make decisions – facilitates evaluation of information
IRM Pathway Translational Research Opportunity Prioritization

- 113 IRM translational research opportunities (various # of components)
- Determined which components were represented in each opportunity
- Added key components from Antigen and IMA prioritization, others added by IRMP WG: 174 final key component candidates
- Ranked each component by:
  - Level of evidence on **Scientific Validity** of each component
    - Experiments in humans
    - Experiments in animals
    - In vitro experiments
  - Information on **Feasibility** of each component
    - Full scale manufacturing
    - Piloted manufacturing
    - Laboratory product
- Each component evaluated by 2-3 IRMP WG members
- Discrepancies discussed and resolved
IRM Pilot Prioritization Project

Translational Science Meetings → Request for Information → NCI-directed Workshops

Translational Research Opportunities

Deconstruct
Key component candidates into buckets

Prioritize
candidates within buckets

Reconstruct
on scaffolds

Targets
Antigens, T-cell targets
Antibody targets

Immune modifying agents
Adjuvants, Checkpoint
Suppressors, T-cell GFs, ADCC

Vaccines, Adoptive therapies
Antibodies, IMA combinations
Immune Response Modifier Pathway Prioritization Working Group Report

November 4, 2009

Martin A. (Mac) Cheever, M.D.
Immune Modifier Agents (IMA)

• Agents that mimic, augment or require participation of host immune cells for optimal effectiveness
Major Issue

- Phenomenal advances in basic immunology
- Discovery and invention of many agents with the potential to serve as immunotherapeutic drugs and cure patients with cancer
  - Many have been manufactured or could readily be manufactured
  - Many have great potential for benefiting cancer patients
    - If they were available for testing &
    - If focused funding were available for clinical trials to learn how to use them
Major Issue

• Cancer vaccine example:
  – Discovered/invented/manufactured agents that could substantially improve cancer vaccines include:
    • Dendritic cell activators & growth factors
    • Vaccine adjuvants
    • T cell stimulators & growth factors
    • T cell attracting agents
    • Inhibitors of T cell checkpoint blockade
    • Inhibitors of immune cell & cancer cell suppression
Major Issue

• Antibody example:
  – Discovered/invented/manufactured agents that could substantially improve antibody therapy include:
    • Agents to increase antibody dependent cellular cytotoxicity (ADCC)
      – NK cell activators & growth factors
      – Dendritic cell activators & growth factors
      – Vaccine adjuvants (active innate immunity)
      – T cell stimulators & growth factors
      – T cell attracting agents
**Immune Response Modifier Pathway**

**Credentialing**
(Antigen Target & Immune Modifier Agent)

**Creation of Modality**
(Antigen + Formulation + Agent)

**Supporting tools**
(Assays to select patients)
(Assays to monitor response)

**Development**
(Scale-up & Manufacturing)

**Clinical Trials**

MANY Antigens & Agents have been moved down the Pathway

“Gap” is insufficient iterative early phase clinical trials to learn how to employ already discovered antigens & agents

[Diagram with flowchart]
“Gap” Barriers

• Concurrent development of several unapproved agents is exceedingly difficult
  – Many immune modifier agents are unlikely to work as monotherapy

• Funding mechanisms support best grants & best groups, not best trials possible

• STRAPS provide a mechanism for designing & funding the best trials possible
  – STRAPS can provide organizational structure & funding mechanisms for
    • Top prioritized trials
      – Access to prioritized standard agents & prioritized novel agents
    • Team of experienced investigators
    • Capacity to elucidate reasons for success or failure
      – Immune response & therapy monitoring
      – Assays for patient selection & correlates of response
    • Adequate “on-time” funding
    • Project management
Categories: Immune Response Modifier Pathway

• Vaccines
  – To activate and expand the number of patient T cells capable of specifically killing cancer cells

• Autologous T cell therapy
  – To treat with large numbers of cultured autologous T cells

• Antibody therapy
  – To augment the efficacy of “standard” antibody therapy

• Combinations of Immune Modifier Agents
  – To activate and expand nascent or ongoing autochthonous immune responses
What vaccine regimen has the highest potential for success?

• Three components of cancer vaccine regimens to consider
  (1) Antigen Target
  (2) Immune modifying agents (IMAs) to induce & maintain immune response
  (3) Regimen
    • Antigen Target in combination with biologically defined IMA

• NCI workshops have piloted prioritization schemes
  – Antigens
    • Cancer Antigen Pilot Prioritization Project (October 2008)
  – Immune modifying agents
    • Immunotherapy Agents Workshop (July 2007)
      – Included adjuvants
  – Regimens (2009)
    • NCI Immune Response Modifier Pathway Prioritization Project
      – To develop an Immune Response Modifier STRAP (Special Translational Research Acceleration Project)
Cancer Antigen Prioritization

Major Criteria with Weighting

- THERAPEUTIC FUNCTION: 0.32
- IMMUNOGENICITY: 0.17
- SPECIFICITY: 0.15
- ONCOGENICITY: 0.15
- EXPRESSION LEVEL & % POSITIVE CELLS: 0.07
- STEM CELL EXPRESSION: 0.05
- NUMBER OF PATIENTS WITH ANTIGEN POSITIVE CANCERS: 0.04
- NUMBER OF EPITOPES: 0.04
- CELLULAR LOCATION OF EXPRESSION: 0.02

Clin Can Res, 15: 5323, 2009
Antigen Pilot Prioritization: Outcome

- None of the 75 antigens had all of the criteria/characteristics of the “ideal” cancer antigen.
- 20 had suggestive clinical efficacy
- 46 were immunogenic in clinical trials
- Outcome
  - Reflected the extent and vigor of the cancer vaccine field
  - Accentuated the need for prioritization.
WT1 Peptide-Based Vaccine – Induces CTL and Regressions in Some Patients

Tumor regression in patient with breast cancer. CAT Scan before (Left) and after (Right) WT1 vaccination

[Oka et al PNAS 101:13885 (2004)]
HER2 Peptide-Based Vaccine

Kaplan-Meier disease-free survival curves at 20 month median follow-up
(171 enrolled patients)

Previously treated disease free at time of vaccination

Planned analysis at 20 months

Randomized on expression of HLA-A2

(P = 0.04) at a median follow-up of 20 months

[Peoples et al Clin Cancer Res 2008;797 14(3) February 1, 2008]
MUC1 Peptide-Based Vaccine: Advanced Stage NSCLC

- Randomized Phase II
- MUC1 peptide vaccine vs. best supportive care
- Stage IIIIB or IV; stable or responding to therapy
- Median survival, 30.6 versus 13.3 months; P = 0.16

[Sangha & Butts Clin Cancer Res 13: 4652s 2007]
MAGE-A3 Protein-Based Vaccine – Randomized Phase II Adjuvant Trial in Early Stage NSCLC

DFS: Interval from the date of surgical resection to the date of recurrence or death.

HR=0.73 (95% CI = 0.45 - 1.16)

one-sided log-rank p= 0.093
What vaccine regimen has the highest potential for success?

• NCI workshops have piloted prioritization schemes
  – Antigens
    • Cancer Antigen Pilot Prioritization Project (October 2008)
  – Immune modifying agents
    • Immunotherapy Agents Workshop (July 2007)
      – Included adjuvants
  – Regimens (Ongoing - 2009)
    • NCI Immune Response Modifier Pathway Pilot Project
      – To develop an Immune Response Modifier STRAP
        (Special Translational Research Acceleration Project)
NCI Workshop to Prioritize Immunotherapy Agents with High Potential for Cancer Therapy (July 12\textsuperscript{th} 2007)

- Developed a ranked list of agents with high potential for use in cancer therapy
  - Exceedingly broad input & well-vetted
- Substantial demonstrated immunological efficacy
- Not broadly available for testing in patients with cancer
- Many already tested in clinical trials in patients with cancer
  - Proven substantial effects in activating, augmenting or sustaining human immune responses
  - Cancer was not eliminated when tested as monotherapy
Basic Tenants of T cell Immunity

• T cell repertoire needs to be infinite
• T cells expansion needs to be strictly limited
  – Limiting T cell growth factor concentration
  – Upregulation of T-cell checkpoint blockade
  – Induction of regulatory/suppressor cells
• Agents to circumvent limitations are available
Prioritization of Agents: List of agents with high potential for cancer therapy

- **T cell growth factors**
  - IL-7 (naïve T cells) [#5]
  - IL-15 (effector T cells) [#1]
  - IL-21 (T cells & NK) [#21]
    - [Not on original list]
- **DC activators**
  - Anti-CD40 & CD40L [#4]
- **DC growth factors to increase body burden of DC**
  - Flt3L [#11]
- **Vaccine adjuvants with immunotherapeutic potential**
  - IL-12 [#3]
  - CpG [#6]
  - MPL [#14]
  - Poly I:C [#15]
  - Resiquimod & 852A [#18]
- **T cell stimulators**
  - 4-1-BB (CD137) [#8]
  - Anti-GITR [#12]
  - Anti-OX40 [#16]
- **T-cell attracting chemokines**
  - Adv-CCL21 [#13]
- **Inhibitors of T cell checkpoint blockade**
  - Anti-PD1 & PD1Ligand [#2]
  - Anti–B7-H4 [#17]
  - Anti–LAG-3 [#19]
  - LIGHT [#20]
- **Inhibitors of cancer cell & immune cell suppression**
  - 1-methyl tryptophan (IDO inhibitor) [#7]
  - Anti-TGF-b [#9]
  - Anti-IL10 & Anti-IL10R [#10]

[Anti-CTLA4 not considered, presumed to be approved in near future]

http://web.ncifcrf.gov/research/brb/site/home.asp
What vaccine regimen has the highest potential for success?

- NCI workshops have piloted prioritization schemes
  - Antigens
    - Cancer Antigen Pilot Prioritization Project (October 2008)
  - Immune modifying agents
    - Immunotherapy Agents Workshop (July 2007)
      - Included adjuvants
  - Regimens (2009)
    - NCI Immune Response Modifier Pathway Pilot Project
      - To develop an Immune Response Modifier STRAP
        (Special Translational Research Acceleration Project)
GOAL: of IRM Pathway Prioritization Working Group
Select “Best” Immunotherapy Regimens for Development

- Cancer vaccines
  - Antigen
  - Adjuvant/Formulation
  - IMA to expand/maintain T cell response (i.e., area under curve - AUC)
  - Assays to monitor outcome – immune response qual & quant /tumor response

- T cell therapy
  - Antigen target
  - Vaccine to expand T cells prior to culture
    - (or recombinant T-cell receptor)
  - Vaccine & IMA post transfer to expand & maintain number of T cells
    - (i.e., area under curve - AUC)
  - Assays to monitor outcome – immune response/tumor response

- Ab therapy
  - Ab
  - IMA to augment ADCC

- IMA Combinations
  - Several synergistic immune response modifiers to activate then augment autochthonous responses
  - Assays to monitor outcome – immune response to specific designated antigens/tumor response
Prioritize candidates within buckets

Deconstruct Key component candidates into *buckets*

Prioritize candidates within buckets

Reconstruct on *scaffolds*

- **Immune modifying agents**
  - Adjuvants
  - Checkpoint
  - T-cell GFs
  - Suppressors
  - ADCC

- **Targets**
  - Vaccine Antigens
  - T-cell targets
  - Antibody targets

- **Vaccines, Adoptive therapies**
- **Antibodies, IMA combinations**

Translational Science Meetings

Request for Information

NCI-directed Workshops

**Translational Research Opportunities**
## Working Group Prioritized Targets & Agents

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>TARGET</th>
<th>IMA <em>(one or more of the following)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Vaccines</td>
<td>A: Vaccine Antigens</td>
<td>D: Adjuvants (required)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E: T-cell factors, and/or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F: Checkpoint inhibitors, and/or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G: Suppressive agents</td>
</tr>
<tr>
<td>Adoptive Therapy</td>
<td>B: T-cell therapy antigens</td>
<td>E: T-cell factors and/or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F: Checkpoint inhibitors</td>
</tr>
<tr>
<td>Antibody Therapy</td>
<td>C: Antibody &amp; T-body antigens</td>
<td>H: ADCC</td>
</tr>
<tr>
<td>IMA Combinations</td>
<td></td>
<td>Combinations of the above</td>
</tr>
</tbody>
</table>
CANCER VACCINE SCAFFOLD

Formulation

Response assay

Patient selection assay

Vaccine & T-cell antigens

Adjuvant

IMA D

T cell factors

IMA E

T cell checkpoint

IMA F

Suppression reversal

IMA G

and

and/or

and/or

Target A
What vaccine regimen has the highest potential for success?

Select a cancer antigen with a high potential for success

• Top 15 antigens from Cancer Antigen Pilot Prioritization Project (Oct 2008)
• Vaccine targets from Response to RFI NOT-CA-09-031
• Vaccine targets from NCI Translational Science meeting abstracts, 2008 and 2009

• Evaluated for Therapeutic Efficacy and Immunogenicity (priority score)
• Further evaluated for appropriateness for STRAP
  – Antigens must be defined
  – Antigens must be represented on enough tumors to accrue patients for clinical trials in a reasonable amount of time
  – Approach should not be “overripe”, i.e. ready for Phase III trials
<table>
<thead>
<tr>
<th>Project</th>
<th>Candidate</th>
<th>Bucket</th>
<th>Rank</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>R028 CpG-MCL vaccine/ATC therapy (lymphoma)</td>
<td>CpG-activated, autologous whole-cell MCL</td>
<td>A</td>
<td>1.00</td>
<td>antigens not defined, patient specific</td>
</tr>
<tr>
<td>R016 Shed BrCa Ag, IL2 GM liposomes</td>
<td>Shed BrCa Ag</td>
<td>A</td>
<td>1.00</td>
<td>antigens not defined</td>
</tr>
<tr>
<td>R006 Auto tumor transfected w IGFR antisense (Astrocytoma)</td>
<td>Auto tumor/IGF-1R/AS ODN</td>
<td>A</td>
<td>1.00</td>
<td>antigens not defined, patient specific</td>
</tr>
<tr>
<td>T1-334 MinorHA alloTcells CD3/CD28/IL2 expand (lymphoma)</td>
<td>MinorHA allo</td>
<td>A</td>
<td>1.00</td>
<td>antigens not defined</td>
</tr>
<tr>
<td>T1-343 MinorHA alloTh2 HSCT</td>
<td>Allogeneic hematologic malignanc shared antigens</td>
<td>A</td>
<td>1.00</td>
<td>antigens not defined, patient specific</td>
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<tr>
<td>T1-342 Unique/shared autoTIL Lymph/deplet IL2 melanoma</td>
<td>Autologous tumor shared antigens</td>
<td>A</td>
<td>1.00</td>
<td>antigens not defined, patient specific</td>
</tr>
<tr>
<td>T2-302 Auto tumor + proteasome inhibitor (NSCLC)</td>
<td>Auto tumor</td>
<td>A</td>
<td>1.00</td>
<td>#4 on antigen list</td>
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<tr>
<td>T1-522 HPV DNA by electroporation</td>
<td>HPV E6/7</td>
<td>A</td>
<td>0.93</td>
<td>HER2</td>
</tr>
<tr>
<td>T1-542 HPV E6/7 DNA + vaccinia (higrade CIN2/3)</td>
<td>HPV E6/7</td>
<td>A</td>
<td>0.93</td>
<td>#6 on antigen list</td>
</tr>
<tr>
<td>A001 HPV E6/E7</td>
<td>HPV E6/E7</td>
<td>A,B</td>
<td>0.93</td>
<td>MAGE A3</td>
</tr>
<tr>
<td>R004 Anti-HER2 fused to LIGHT protein</td>
<td>HER2</td>
<td>A</td>
<td>0.90</td>
<td>#8 on antigen list</td>
</tr>
<tr>
<td>T2-030 Allo tumor/GM + Cy + Doxorubicin (BrCa)</td>
<td>HER2</td>
<td>A</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>T1-546 HER2 Adv (EC +TM domain) + DC for BrCa</td>
<td>HER2</td>
<td>A</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>T2-154 HER2 heterologous DNA</td>
<td>HER2 heterologous DNA</td>
<td>A</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>A002 HER-2/neu</td>
<td>HER2</td>
<td>A,B</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>A003 MAGE A3</td>
<td>MAGE A3</td>
<td>A</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td>T2-112 MelanA/MART1 recombTCR + PET reporter</td>
<td>MelanA/MART1</td>
<td>A</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>A004 MelanA/MART1</td>
<td>MelanA/MART1</td>
<td>A,B</td>
<td>0.85</td>
<td></td>
</tr>
<tr>
<td>A014 gp100</td>
<td>gp100</td>
<td>A,B</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>R034 gp100/OX40mAB/HD IL-2 (melanoma)</td>
<td>gp100+Trp2</td>
<td>A</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>R039 gp100/Trp2 + Hsp110 complex (melanoma)</td>
<td>gp100+Trp2</td>
<td>A</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>T1-545 Heterol gp100/TYRP2/GM-CSF DNA particle</td>
<td>Heterol gp100/TYRP2</td>
<td>A</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>R025 Melanoma peptide-pulsed IL-15DC for melanoma/IL7 (MART-1+ gp100+ MAGE-A3+ tyrosinase)</td>
<td>MART-1+ gp100+ MAGE-A3+ tyrosinase</td>
<td>A</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>T2-226 Adv Tyrosinase/MART1/MAGE-A6 + DC</td>
<td>Adv Tyrosinase+MART1+MAGE-A6</td>
<td>A</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>A008 MUC1</td>
<td>MUC1</td>
<td>A,B</td>
<td>0.84</td>
<td>#5 on antigen list, not included because small subset of patients</td>
</tr>
<tr>
<td>T1-530 MUC1 peptides w Tn carbohydrate (BrCa)</td>
<td>MUC1</td>
<td>A</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>T1-538 EGFvIII peptide vac + temozolomide (GBM)</td>
<td>EGFvIII</td>
<td>A</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>A005 EGFvIII protein</td>
<td>EGFvIII</td>
<td>A</td>
<td>0.84</td>
<td></td>
</tr>
</tbody>
</table>
Working Group Prioritized Targets & Agents

• **A: Vaccine Targets**
  – HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA

• **B: T-Cell Therapy Targets:**
  – HER2, HPV E6/7, MUC1, MAGE A3, WT1, NY-ESO-1, PSA

• **C: Antibody & T Body Targets**
  – HER2, EGFR, CD20, CD19

• **D: IMA: Vaccine adjuvants, dendritic cell activators, T cell attracting chemokines, or DC growth factors**
  – CpG, CD40, IL-12

• **E: IMA: T cell stimulators or T cell growth factors**
  – IL7, IL21, IL15, Anti-4-1BB

• **F: IMA: Inhibitors of T cell checkpoint blockade**
  – Anti-CTLA-4, Anti-PD1

• **G: IMA: Agents to neutralize or inhibit suppressive cells, cytokines, and enzymes**
  – Anti-TGF beta, IDO inhibitors, Anti-IL10

• **IMA H: Agents to increase antibody dependent cellular cytotoxicity (ADCC)**
  – IL7, CpG, Anti-CD40, IL12, Anti-4-1BB or chimeric antibody receptors (CAR)
CANCER VACCINE SCAFFOLD

Formulation

Vaccine & T-cell antigens
Target A

Patient selection

Response assay

Patient selection assay

Adjuvant
IMA D

and

T cell factors
IMA E

and/or

T cell checkpoint
IMA F

and/or

Suppression reversal
IMA G
HPV Vaccine – Antibody Response

HPV-16

Antibodies (GMT)

Day 210

Alum + MPL (Monophosphoryl Lipid A)

[Alum alone]

[JP Garnier, GSK CEO, Corporate Media Presentation Feb, 2005]
D: IMA: Vaccine adjuvants, dendritic cell activators, T cell attracting chemokines, or DC growth factors

- Adjuvants
  - Mandatory to achieve highest levels of response
    - Many choices
    - Best not defined
    - No “standard” adjuvant regimen
    - Dearth of adequate adjuvants for current trials

- NCI Agent Workshop provided list of 20 priority IMAs
  - 8 of 20 were deemed effective adjuvants

- Four prioritized by IRMP Working Group
  - Anti-CD40 & CD40L (DC Activator)
  - IL-12 (Vaccine Adjuvant)
  - CpG (Vaccine Adjuvant)
  - CCL21 (T cell attracting chemokine)

- Others on NCI Agent Workshop list
  - IL7, Flt3L, MPL, poly I:C, resiquimod

- Adjuvants need to be supplied to most investigators
  - Will require iterative human in vivo testing for most antigen formulations
Working Group Prioritized Targets & Agents

Select an adjuvant with a high potential for success

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CANCER VACCINE SCAFFOLD

- Formulation
- Patient selection
- Response assay
- Patient selection assay

- Vaccine & T-cell antigens
  - Target A

- Adjuvant
  - IMA D

- T-cell factors
  - IMA E

- T-cell checkpoint
  - IMA F

- Suppression reversal
  - IMA G

Options:
- and
- and/or
Working Group Prioritized Targets & Agents

Select an IMA with a high potential for success

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“Administration of rhIL-7 in humans increases in vivo TCR repertoire diversity by preferential expansion of naive T cell subsets”

IL-7 administered every other day (days 1 – 14) at 4 dose levels

IL-7 therapy increases circulating T cells

PET-CT imaging of lymphoid organs & increased metabolic activity after rhIL-7

Day 14   Day 56

Increased metabolic activity = pink  Maximal = yellow

[Sportès (Mackall) et al J. Exp. Med. 1681:2007]
4-1BB (CD137)

• Co-stimulatory receptor on T cells
  – Induced upon T-cell receptor (TCR) activation

• Agonist Ab (anti-CD137) leads to
  – Increased T-cell proliferation
  – Cytokine production
  – Functional maturation
  – Prolonged CD8 T-cell survival
Tumor-involved lymph nodes from lymphoma patients are infiltrated by CD137 T cells

[Houot et al (Levy) BLOOD 114:3431 2009 ]
Anti-CD137 agonistic mAb has potent antilymphoma activity in vivo

BALB/c mice inoculated subcut with $5 \times 10^6$ A20 tumor cells

[Houot et al (Levy) BLOOD 114:3431 2009]
ADOPTIVE THERAPY SCAFFOLD

- Formulation
- T-cell therapy targets Target B
- Response assay
- Patient selection assay
- T-cell factors IMA E
- T-cell checkpoint IMA F

and/or

Prefer recombinant T cell receptor
Plus vaccine to maintain T cell survival post therapy
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ANTIBODY SCAFFOLD

Formulation

Response assay

Patient selection assay

Antibody & T body targets Target C

Patient selection

ADCC

IMA H

Prefer Approved Ab plus IMA
Six Approved Antibodies Mediate Effects, in part, through Antibody Dependent Cellular Cytotoxicity (ADCC)

- Ab binds to cancer cell
- Fc portion of Ab binds to Fc Receptor on WBC
- WBC apposed to cancer cells kill cancer cells
- Degree of killing depends on level of binding.

ADCC: Antibody-Dependent Cell-mediated Cytotoxicity

ADCC is a major mechanism for killing tumor cells by therapeutic antibodies
Antibody Target

• At least 3 commonly used FDA approved antibodies require, in part, host participation, i.e. antibody dependent cellular cytotoxicity (ADCC) for optimal therapy
  – Rituximab (anti-CD20)
  – Cetuximab (anti-EGFR)
  – Trastuzumab (anti-HER2/neu)
ADCC is an Important Mechanism for Herceptin Function:
Progression free survival depends on level of binding of Fc portion to Fc receptors on NK cells

**Background:** FcR valine (V/V) polymorphism is more effective than phenylalanine (F) in mediating ADCC

- **V/V polymorphism = Increased FcRγ III binding**

![Graph showing progression free survival](chart.png)

- **V/V** polymorphism: Not reached
- **V/F** polymorphism: 15.0 (P = .008)
- **F/F** polymorphism: 11.1 (P = .005)
- **F carriers**: 12.9 (P = .0035)

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  - IL7, CpG, Anti-CD40, IL12, Anti-4-1BB or chimeric antibody receptors (CAR)
Rational Sequence

(1) IMA to activate autochthonous T cell responses

(2) IMA to expand & maintain T cell response
RECOMMENDATION

• Four STRAPs representing three scaffolds
  – Vaccine: Viral antigen
  – Vaccine: Self cancer antigen
  – Adoptive Cellular therapy
  – Antibody therapy

• NCI “anchor” at least one of two buckets
  – E: IMA: T cell stimulators or T cell growth factors
    • IL7, IL21, IL15, Anti-4-1BB
  – F: IMA: Inhibitors of T cell checkpoint blockade
    • Anti-CTLA-4, Anti-PD1

• NCI provide adjuvant
  – From Immunotherapy Agents Workshop

• Call for applications for Targets side of scaffold
Adjuvants provided by NCI
Why is this approach to investigator-driven translational research necessary?
Submitted Translational Research Opportunity:
HPV 16/18 E6/E7 DNA prime: Vaccinia boost (CIN3)

[Goal: Develop effective therapy that can be tested and used at multiple institutions]

• Deconstruction and restructure
  – DNA prime
  – Provide adjuvants for DNA prime (not commonly available)
    • CpG or CD40,
  – Boost with recombinant vaccinia
    • Effective, but repeated vaccination limited due to vaccinia specific immunity
  – Provide adjuvants for DNA boosting to allow repeated vaccination
    • CpG or CD40,
  – Provide IMA to augment & sustain response
    • T cell growth factor (IL7) or
    • T cell stimulator (Anti- 4-1BB)
Submitted Translational Research Opportunity: MART-1, gp100, MAGE-A3, tyrosinase peptides: Dendritic cells as adjuvants

Goal: Develop effective therapy that can be tested and used at multiple institutions

• Deconstruction and restructure
  – MAGE-A3 only (priority antigen)
  – Provide alternative formulation (non-DC)
    • Provide adjuvants for alternative formulation
    • CpG or IL-12
  – Provide IMA to augment & sustain response
    • T cell growth factors
      – IL15
    • Inhibitors of T cell checkpoint blockade
      – Anti-CTLA-4
    • Agents to neutralize or inhibit suppressive cells, cytokines, and enzymes
      – Anti-TGF beta
Submitted Translational Research Opportunity: TIL therapy of melanoma with myelosuppressive conditioning + IL2

Goal: Develop effective therapy that can be tested and used at multiple institutions

• Deconstruction and restructure
  – **Vaccine** prior to in vitro T cell growth
    • Or, Recombinant TCR
  – Target with restricted distribution vs. TIL
    • T-Cell Therapy Targets:
      – **NY-ESO-1**
    • T-Body Targets
      – **CD19**
  – T cell growth factors post transfer
    • **IL7, IL15 or IL21**
  – **Vaccine post transfer**
Submitted Translational Research Opportunity:
Therapy with antibody to GD2 with IL2
Goal: Develop effective therapy that can be tested and used at multiple institutions

• Deconstruction and restructure
  – Commercial antibody known to function in part via antibody dependent cellular cytotoxicity (ADCC)
  – Supply agents known to increase ADCC for iterative early phase trials
    • IL7, CpG, Anti-CD40, IL12, Anti-4-1BB
  – Move best results into randomized Phase III with cooperative groups
The Translational Research Acceleration Initiative

Clinical Trials and Translational Research Advisory Committee
November 4, 2009

Lynn M. Matrisian
Special Assistant, NCI
IRM Pilot Prioritization Project

113 Opportunities
174 key component candidates

Scientific Prioritization

Limited # scaffolds with prioritized candidates in buckets
Recommended priority scaffolds and buckets

Clinical Trials and Translational Research Advisory Committee (Extramural) Nov 4, 2009
IRM Pilot Prioritization Project: NEXT STEPS

Scientific Prioritization

Recommended scaffolds and buckets

NCI Prioritization:

- Logistical feasibility
- Clinical Need
- Appropriateness for NCI investment

Select candidate(s) from IMA bucket(s) as anchor
Select Target bucket(s) for competition

Complete by December 2009
Top IMA candidate(s) and top target bucket(s)

Develop 1-4 IRM Special Translational Research Acceleration Project (STRAP) concepts

NCI Leadership

Advisory boards as appropriate

Request(s) for Supplements/Proposals/Applications
Process to Accelerate Translational Science Initiative

1. Gather information
2. Prioritize
3. Fund & Manage
Special Translational Research Acceleration Projects (STRAPs)

- Requirements:
  - Goal of completing early stage human studies
  - Project management plan
  - Specific development milestones and timelines
  - Development/commercialization strategy
- Funds for new and/or expanded projects
- Project management would link new or existing teams and projects and facilitate hand-offs between groups
- Opportunities to include industry/foundation funding or participation
Call for Supplements/Applications/Proposals for 1-4 IRM STRAPS

Scientific/Feasibility Review using Criteria set for remaining IRM components:
- Formulation
- Combination
- Assay for response
- Assay to select pts
- Availability pts for clinical trials

Supplements/existing mechanisms:
- NeXT
- R01
- Cooperative Groups
- P01
- RAPID
- EDRN
- SPOREs
- Cancer Centers
- etc

New (if necessary):
- RFPs
- RFAs
- Cooperative Agreements
- CRADAs
- etc

NCI leadership

Advisory board as appropriate

Funded STRAP

FY2010
Determine pathway-specific criteria

Fall 2009
- Immune Response Modifier

Winter 2009/2010
- Agents
- Biospecimens
- Lifestyle Alterations

Spring 2010
- Imaging
- Interventive Devices

Pilot Projects for each of the Pathways

Therapeutic intent:
In conjunction with NCI Experimental Therapeutics Program
Staging of Process to Accelerate Translational Science (PATS) Subgroups

- **Fall 2009**
  - **Immune Response Modifier**

- **Winter 2009/2010**
  - **Agents**
    - Therapeutic intent: In conjunction with NCI Experimental Therapeutics Program
  - **Biospecimens**
  - **Lifestyle Alterations**

- **Spring 2010**
  - **Imaging**
  - **Interventive Devices**
Consistent with TRWG underlying principles

• Evaluate the status of NCI’s investment in translational research & envision its future in an inclusive, representative & transparent manner
• Overcome barriers resulting from the dispersal of translational research throughout the NCI DOC’s
• Change: “business as usual” is untenable
• Will it accelerate translational cancer research? Evaluation in planning stage
IRMP WG Report: RECOMMENDATIONS

• Four STRAPs representing three scaffolds
  – Vaccine: Viral antigen
  – Vaccine: Self cancer antigen
  – Adoptive Cellular therapy
  – Antibody therapy

• NCI “anchor” at least one of two buckets
  – E: IMA: T cell stimulators or T cell growth factors
    • IL7, IL21, IL15, Anti-4-1BB
  – F: IMA: Inhibitors of T cell checkpoint blockade
    • anti-CTLA-4, Anti-PD1

• NCI provide adjuvant
  – From Immunotherapy Agents Workshop

• Call for applications for Targets side of scaffold
• Target antigens in buckets represent high priority examples
  – HPV E6/E7, HER2, MAGE A3, MUC1, WT1, NY-ESO-1, PSA
• Applications are not restricted to these targets
• Submitted targets must demonstrate equivalency to priority candidates in scientific validity and feasibility
• Applications address remaining critical components of scaffold
  – Formulation
  – Assay for immune response
  – Assay to select patient population
  – Availability of patients for clinical trials

• Are reviewed using pre-determined and pre-weighted criteria and subcriteria
  – All of above
  – Combination regimen
• NCI makes choice of IMA anchors based on logistical feasibility
• NCI decisions on reviewed applications take into account:
  – Clinical need
    • Rare diseases
    • Immunoprevention
  – Appropriateness for NCI investment
    • Redundancy with industry
• Immune Response Modifier Special Translational Research Acceleration Projects be launched, reviewed, and funded in FY2010
• DISCUSSION

• Does CTAC accept the IRMP WG report and recommendations?